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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/444,281 | 11/19/1999 | JAN BURIAN | 660081.411 | 8461 |

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| EXAMINER | |
|---|---|
| SCHNIZER, HOLLY G | |
| ART UNIT | PAPER NUMBER |
| 1653 | |

DATE MAILED: 01/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/444,281 | BURIAN ET AL. | |
| | Examiner | Art Unit | |
| | Holly Schnizer | 1653 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for R ply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,4,12,13,15-18,20,29,31,32,35-37,40-42,44,45 and 47-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,12,13,15-18,20,29,31,32,35-37,40-42,44,45 and 47-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 September 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

### *Status of the Claims*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 6, 2002 has been entered.

Upon entry of the RCE, the Amendment filed September 9, 2002 has now been entered. Claims 30, 33, 34, 38, 39, 43, and 46 have been canceled and Claims 54-64 have been added. Therefore, Claims 1, 2, 4, 12, 13, 15-18, 20, 29, 31, 32, 35-37, 40-42, 44-45, and 47-64 are pending.

### *Drawings*

The drawings filed 09/09/02 have been approved by the draftsperson.

### *Declaration*

Upon Applicants request, The Declaration of Burian and Bartfeld under 37 CFR 1.131 (filed December 17, 2001 as Paper No. 14) and attached Exhibit, submitted in response to the prior art rejection over Zhang et al., has been reconsidered in light of Applicants arguments. The Exhibit states that a cassette was prepared "containing MBIII (no stop codon) followed by a 8 amino acid (25 base pair) fragment, the spacer. This particular spacer is a natural sequence from Apis mellifera (honeybee); it occurs

between identical copies of genes producing apidaecins. Hopefully, the spacer will have a similar effect to its natural version" (see p. 1 of Exhibit of Paper No. 14). Applicants indicate that the spacer sequence referred to in the Declaration is anionic (p. 6 of Paper No. 20). Therefore, the exhibit provides evidence that a construct using, specifically, the spacer from *Apis mellifera,* which is anionic, was contemplated. However, the Declaration does not appear to provide any evidence that the spacer from *Apis mellifera* was selected because of its anionic nature.

As explained below in the withdrawal of the obviousness rejection, the Exhibit provides laboratory pages showing a construct including the T7 promoter and the Declaration implies that the construct shown in the laboratory pages was contemplated prior to 1998.

***Objections and Rejections Withdrawn***

The rejection of Claims 29-53 under 35 U.S.C. 112, first paragraph is withdrawn in light of the amendment to the claims.

The rejection of Claim 29-53 under 35 U.S.C. 112, second paragraph, as being indefinite as to the metes and bounds of the position of the cleavage site between the cationic peptide and the carrier, is withdrawn in light of the amendment to the claims.

The rejection of Claim 33 under 35 U.S.C. 112, second paragraph for failing to further limit Claim 29 is withdrawn in light of its cancellation.

The rejection of Claim 34 under 35 U.S.C. 112, second paragraph, as confusing as to how "the carrier" can be located at the C-terminus of the fusion protein when

Claim 29, from which Claim 34 depends, indicates that "the carrier" is located at the N-terminus (see line 8 of Claim 29), is withdrawn in light of the cancellation of this claim.

The rejection of Claim 44 under 35 U.S.C. 112, second paragraph, for the omission of a sequence identifier to define the sequence provided in the claim, is withdrawn in light of the amendment to the claim.

The rejection of Claim 46 under 35 U.S.C. 112, second paragraph is withdrawn in light of the amendment to the claim.

The rejection of Claim 15 under 35 U.S.C. 103(a) ) as being unpatentable over Better (ref. AB of IDS of Paper No. 16) in view of Zhang et al. (Biochem. Biophys. Res. Comm. (1998) 247: 674-680; Ref. AP of IDS of Paper No. 11) is withdrawn in view of the Declaration of Burian and Bartfeld under 37 CFR 1.131 (filed December 17, 2001 as Paper No. 14) and attached Exhibit indicating that a construct with a T7 promoter was contemplated before 1998 and therefore before the Zhang et al. publication. However, it is noted that the promoters listed in Claim 15 were very well known in the art at the time of the invention as evidenced by the rejection below using new references.

***Rejections Maintained***

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in-

> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 1, 2, 4, 16, 17, 18, and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Better (U. S. Patent No. 5,851,802; reference AB in IDS of Paper No. 16).

Applicants argue that Better fails to teach or suggest a fusion protein construct including indolicidin analogs. This argument has been considered but is not deemed persuasive because the claims are unclear as to what is considered an "analog" and thus the BPI peptide described in Better is considered an "analog" of indolicidin.

Better discloses a multi-domain fusion protein expression cassette, comprising a promoter operably linked to a nucleic acid molecule which is expressed as an insoluble protein (see Col. 22, line 55), wherein the nucleic acid molecule encodes a polypeptide comprising the structure (cationic peptide)[(cleavage site)-(cationic peptide)]$_n$ wherein n has a value of up to 4 (see Fig. 5 and Col. 8, lines 43-45 showing up to 5 peptide repeat units). Better indicates that the preferred structure of the cassettes contains a carrier protein as exemplified by 5'-(nucleic acid molecule encoding carrier)-(cleavage site )-(nucleic acid molecule encoding at least one cationic peptide)-3' (see Col. 7, lines 58-67) and that the carrier peptide may also be a cationic peptide (Col. 8, line 7-10). Better teaches that the cleavage sites may be cleaved by acid hydrolysis (low pH)(Col. 20,

lines 22-23). The examples of Better teach that the disclosed vectors containing the expression cassettes can be transformed into *E. coli* host cells in a method of expressing of the fusion proteins that contain the cationic peptides (See Example 2, Col. 16 and Example 3). The cationic peptide in the expression cassettes disclosed in Better is the antimicrobial BPI peptide (see Col. 7) which is considered an indolicidin analog (analogs considered cationic peptides that have antimicrobial activity). Thus, the rejection is maintained.

***New Rejections***

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Better (ref. AB of IDS of Paper No. 16) in view of Shen et al. (Proc. Natl. Acad. Sci. (1984) 81: 4627-4631; ref. BH of IDS of Paper No. 9), Stratagene Catalog (1993; pp38, 44, and 48), the Pharmacia Product Catalog (1996; pp. 110 and 121-123), and Sambrook et al. (Molecular Cloning: A laboratory Manual, 1989, Cold Spring Harbor Laboratory Press, p. 1.14-1.15).

2. Better discloses a multi-domain fusion protein expression cassette, comprising a promoter operably linked to a nucleic acid molecule which is expressed as an insoluble protein (see Col. 22, line 55), wherein the nucleic acid molecule encodes a polypeptide comprising the structure (cationic peptide)[(cleavage site)-(cationic peptide)]$_n$ wherein n has a value of up to 4 (see Fig. 5 and Col. 8, lines 43-45 showing up to 5 peptide repeat units). Better teaches that the highest yield of product comes from a vector containing an expression cassette with four cationic peptide repeat units (Col. 8, lines 43-45 and Fig. 5). Better indicates that the preferred structure of the cassettes contains a carrier protein as exemplified by 5'-(nucleic acid molecule encoding carrier)-(cleavage site )-(nucleic acid molecule encoding at least one cationic peptide)-3' (see Col. 7, lines 58-67) and that the carrier peptide may also be a cationic peptide (Col. 8, line 7-10). As explained above, the cationic peptide in the expression cassettes disclosed in Better is the antimicrobial BPI peptide (see Col. 7) which is considered an indolicidin analog (analogs considered cationic peptides that have antimicrobial activity).

3. Better uses the araB promoter in the constructs disclosed therein. Better does not teach that the expression cassette has one of the promoters claimed in Claim 15.

4. Shen et al. teach that lac and tac promoters can be used successfully in the high level expression of proteins from cassettes containing multiple copies of coding sequences.

5. The Stratagene catalog, Pharmacia catalog, and Sambrook et al. provide evidence that the promoters listed in claim 15 were well known in the art and readily available at the time of the invention.

MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In the instant case, Shen et al., Sambrook et al., and the Pharmacia and Stratagene catalogs teach that there are a variety of promoters that can be used in the recombinant expression of proteins. As evidenced by Shen et al., Sambrook et al., and the Pharmacia and Stratagene ., the promoters of Claim 15 were well known in the art and readily available at the time of the invention. A person of ordinary skill in the art would have recognized the interchangeability of the promoter of the prior art for the promoters of Claim 15. The prior art promoter performs the identical function (promote transcription) as the claimed promoters in substantially the same way. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to have replaced the promoter disclosed in Better for one of the promoters described in Current Protocols. One would have had motivation to change the promoter depending on the materials (host cells, vectors, induction materials such as IPTG) available in the laboratory. Thus, the claims are unpatentable over the prior art.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4, 12, 13, 15-18, 20, 29, 31, 32, 35-37, 40-42, 44-45, and 47-64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to

particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 29 have been amended to recite an expression cassette that contains an "indolicidin analog". The metes and bounds of the claims are not clear because the specification only provides one sequence for Indolicidin and does not provide any definition as to what sequences are considered "indolicidin analogs". How many modifications in the indolicidin sequence can be made before the peptide ceases to be an indolicidin peptide? Is an indolicidin analog considered any peptide that is cationic or any peptide that has antimicrobial activity or both? Or, must the analog have a certain similarity in sequence to a particular indolicidin sequence? Clarification is required. Claims 2, 4, 12, 13, 15-18, 20, 31, 32, 35-37, 40-42, 44-45, and 47-64 are also rejected since they depend from these rejected base claims yet do not correct their deficiencies.

The recitation of "at least one indolicidin analog in Claims 20 and 50 is indefinite because the claims from which they ultimately depend (clms 1 and 29 respectively) specifies an expression cassette that would produce at least two indolicidin analogs within the fusion protein. Correction is required.

Claims 41 and 42 are unclear as to the metes and bounds of "about". The number of proteins in a fusion protein sequence is a definite number and the specification fails to define how many indolicidin analogs are encompassed by the term "about". Therefore, the metes and bounds of the claims are unclear. Correction is required.

Claim 41 is also unclear as to the position of the indolicidin analogs relative to the fusion protein. Are these 5-30 indolicidin analogs in addition to those recited in the construct of Claim 29? Or, are the 5-30 indolicidin analogs defining what the value of "n" is in the formula provided in Claim 29? If the latter is correct, then amending the claim to state "wherein n has a value of between 5 and 30" (or "between 10 and 20" for Claim 42) would overcome this rejection.

***Conclusions***

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Holly Schnizer
January 22, 2003

CHRISTOPHER S. F. LOW
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